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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/614,116	07/03/2003	Colin M. Tice	A9535	3335

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EXAMINER	
POPA, ILEANA	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/614,116	**Applicant(s)** TICE ET AL.	
	Examiner Ileana Popa	**Art Unit** 1633	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 26 February 2007 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires 4 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: 6-17.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☒ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: see continuation sheet.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

Ileana Popa

Joe Woitach
AU1633

Claims 6-17 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Martinez et al. (Mol Gen Genet, 1999, 261: 546-552), in view of both Dhadialla et al. (Annu Rev Entomol, 1998, 43: 545-569) and Saez et al. (Proc Natl Acad Sci USA, 2000, 97: 14512-14517), as evidenced by Guan et al. (Journal of Combinatorial Chemistry, 2000, 2: 297-300) and Michelotti et al. (U.S. Patent No. 5,304,572) for the reasons of record set forth in the prior Office actions.

Applicant argues that:

(i) Martinez et al. and Saez et al. taken alone or together teach only that some diacylhydrazine compounds acting as EcR agonists are also capable of activating an EcR-based gene expression system and are silent with respect to other compounds that might be useful as EcR agonists or for gene switch activation; therefore, these references, ar best, suggest to one of ordinary skill in the art to randomly test diacylhydrazine compounds, but they provide no motivation or guidance towards any other particular structure or compound;

(ii) although Dhadialla et al. teach that DTBHIB can act as an EcR agonist with a potency similar to RH-5849, a known diacyldydrazine pesticide, they indicate that its ability to act as a pesticide is unknown;

(iii) DTBHIB does not contain a ketone group that is critical for the claimed compounds and it is imporper to use the claimed compounds to decide it would have been obvious to make derivatives of DTBHIB that are encompassed by the present claims and the proper question is whether one of skill in the art reading Marinez et al., Saez et al., and Dhadialla et al. would find a teaching, suggestion or motivation to modify DTBHIB to add a ketone structure with a reasonable expectation that the resulting derivative would be an activator of the EcR-based gene expression system;

(iv) building a combinatorial library around the central core of DTBHIB would not produce the present compounds because the central core of DTBHIB does not contain the essential ketone moiety and the removal of the ketone moiety from the compounds eliminates activity;

(v) in the absence of any knowledge that DTBHIB has the ability to act as a gene switch activator, it would not have been obvious to derivatize it with the hope of producing switch activators;

(vi) Guan et al. do not remedy the defieciency of Martinez et al., Saez et al., and Dhadialla et al. because they teach a technique of buiding combinatorial libraries around a core structure, and do not teach EcR agonists or DTBHIB;

(vii) the compound of Michelotti et al. and DTBHIB do not share sufficient close structural similarity to have an expectation of similar properties as they are not position isomers or homologs of each other and the same is true for DTHBHIB as compared to diacylhydrazine EcR agonists;

(viii) Applicant attaches Mikitani (Biochem Biophys Res Commun, 1996, 227: 427-432), wherein Mikitani, the first to disclose DTBHIB, teaches that a very closely related compound differing from DTBHIB only by having an isopropyl side cahin instead of isobutyl does not bind to EcR. Therefore, Applicant submits that even slight changes to the DTBHIB structure can destroy EcR agonist activity and tehrefore, the compounds of Michelotti et al. would not be reasonable expected to be EcR agonists just because they look somewhat similar to DTBHIB.

Applicant's arguments are acknowledged, however, they are not found persuasive for the following reasons:

(i) In response to applicant's arguments against the Marinez et al. and Saez et al., one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. It is noted that the instant rejection is based ion the combined teachings of Marinez et al., Saez et al., and Dhadialla et al.;

(ii) the fact that Dhadialla et al. teach that DTBHIB ability to act as a pesticide is unkown is irrelevant, because they do teach that DTBHIB is an EcR agonist with activity similar to RH-5849; since RH-5849 is used as agene switch activator, one of skill in the art would have readily recognize that DTBHIB could also be an activator of EcR-based inducible gene expresion systems. It is noted that even Mikitani (the reference provided by the Applicant) teaches that DTBHIB has the ability to efficiently activate EcR-based inducible gene expression systems (p. 428, Results, p. 4229, Fig. 1 and 2, p. 431, Discussion, first paragraph);

(iii) and (iv) Applicant's argument that the ketone group is critical for activity is just an argument that is not supported by any evidence. The art of evidence does not support such an argument. It is noted that, although, DTBHIB does not contain a ketone group, it does efficiently activate the EcR-based gene expression system. Furthermore, Dhadialla et al. teach EcR agonists wherein the ketone group is present (p. 549, Fig. 1) and therefore, one of skill in the art would have known that the addition of a ketone group would not impair the activity and would have been able to produce the claimed compounds and build a combinatorial libray, wherein some compounds would contain the ketone group. It is noted that one of skill in the art would know how to screen such libraries for potent agonist and would know that such screening would require nothing more than routine experimentation;

(v) As indicated above, both Dhadialla et al. and Mikitani teach that DTBHIB has the ability to act as a gene switch activator and therefore it would have been obvious to one of skill in the art to further derivatize it in order to produce switch activators. Moreover, even if he teaches that one change does not lead to an active compound, Mikitani clearly teaches the necessity of chemical modifications of DTBHIB to obtain more potent EcR agonists (p. 431, third paragraph);

(vi) Guan et al. do not have to teach compounds similar to the ones claimed. Ther reference was cited to demonstrate that building libraries around a lead compound and screening these libraries was routine in the art at the time the invention was made. One of skill in the art would have understood that somer modification might result in less potent compounds or compounds without activity; however, as as mentionedabove, this determination could be done by routine experimentation;

(vii) Applicant argues that a prima facie case obviousness based on close structural similarity bvetween chemical compounds is appropriately made only when the compounds are exceedingly close in structure that one would expect the compound to have similar properties and that the only examples of sufficient structural similarity in the MPEP are position isomers and homologs (i.e., compounds differing by the successive addition of the same chemical groups, e.g., by -CH2- groups) and that the compounds of Michelotti et al. and DTBHIB do not share sufficient close structural similarity to have an expectation of similar properties because they are not position isomers or homologs of each other. It is noted that MPEP 2144.09 clearly states that the prior art structures do not have to be true homologs or isomers to render structurally similar compounds prima facie obvious. Additionally, thew two compounds are very similar, with the exception that DTBHIB lacks a ketone group. However, Dhadialla et al. teach that the presence of the ketone group in some EcR agonists (see above). Based on these teachings, one of skill in the art would have exxpected that the compound of Michelotti et al. would also be an EcR agonist and would have been motivated to screen it for its capacity of inducing gene expression from EcR-based inducible systems;

(viii) Regarding Mikitani, it is noted that the reference does not teach against modifications of DTBHIB shemical structure. On the

contrary, they teach the necessity of introducing such modifications for obtaining more potent compounds and they expect that such modification would be reasonably expected to render EcR agonists (see p. 431, Discussion). Even if some modifications would render inactive compounds, these compounds can be easily weed out by routine experimentation (see above). Moreover, based on the teachings of Dhadialla et al. , one of skill in the art would reasonably expect that the compound of Michelotti et al. would be an EcR agonist (see above).